

EXHIBIT 1

(Part 1 of 3)

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Fodor et al.

(10) **Patent No.:** **US 6,355,432 B1**
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(54) **PRODUCTS FOR DETECTING NUCLEIC ACIDS**

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435/288.3; 530/300; 530/350; 530/387.1;
536/23.1; 536/24.3

(58) **Field of Search** **536/23.1, 24.3;**
435/6, 287.2, 288.3, 7.1; 530/300, 350,
387.1

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|-------------|---------|------------------|-------------|
| 3,730,844 A | 5/1973 | Gilbam et al. | 195/103.5 R |
| 3,849,137 A | 11/1974 | Barzynski et al. | 96/97 |
| 3,862,056 A | 1/1975 | Hartman | 252/511 |
| 3,939,350 A | 2/1976 | Kronick et al. | 250/365 |
| 4,072,576 A | 2/1978 | Arwin et al. | 195/103.5 R |
| 4,121,222 A | 10/1978 | Diebold et al. | 347/7 |
| 4,180,739 A | 12/1979 | Ahu-Shumays | 250/461 R |
| 4,216,245 A | 8/1980 | Johnson | 427/2.13 |
| 4,238,757 A | 12/1980 | Schenck | 357/25 |
| 4,269,933 A | 5/1981 | Pazos | 430/291 |
| 4,314,821 A | 2/1982 | Rice | 23/230 B |
| 4,327,073 A | 4/1982 | Huang | 424/1 |
| 4,339,528 A | 7/1982 | Goldman | 430/323 |
| 4,342,905 A | 8/1982 | Fujii et al. | 250/201 |
| 4,373,071 A | 2/1983 | Itakura | 525/375 |

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

| | | |
|----|---------|--------|
| CA | 1284931 | 6/1991 |
| DE | 2242394 | 3/1974 |
| DE | 3440141 | 5/1986 |
| DE | 3505287 | 3/1988 |
| EP | 046 083 | 2/1982 |
| EP | 088 636 | 9/1983 |

| | | |
|----|---------|---------|
| EP | 103 197 | 3/1984 |
| EP | 127 438 | 12/1984 |
| EP | 063 810 | 3/1986 |
| EP | 174 879 | 3/1986 |
| EP | 194 132 | 9/1986 |
| EP | 228 075 | 7/1987 |
| EP | 245 662 | 11/1987 |
| EP | 268 237 | 5/1988 |
| EP | 130 523 | 6/1988 |

(List continued on next page.)

OTHER PUBLICATIONS

Brenner et al., "In vitro cloning of complex mixtures of DNA on microbeads: Physico-chemical separation of differentially expressed cDNAs", *PNAS*, 02/2000, 97:665-1670.

Brenner et al., "Gene expression analysis by massively parallel signature sequencing (MPSS) on microbead arrays", *Nature Biotechnol.*, 06/2000, 18:630-634.

Tyagi, "Taking a census of mRNA populations with microbeads", *Nature Biotechnol.* 06/2000, 18:597-598.

Miller et al., "Detection of bacteria by hybridization of rRNA with DNA-latex and immunodetection of hybrids" *J Clin Microbiol* 1988, 26:1271-1276.

Sequencing by Hybridization Workshop, listing of participants and workshop presentation summaries, from workshop held 11/19-20/91.

"A Sequencing Reality Check," *Science*, 242:1245 (1988).

"Affymax raises \$25 million to develop high-speed drug discovery system," *Biotechnology News*, 10(3):7-8 (1990).

"Preparation of fluorescent-labeled DNA and its use as a probe in molecular hybridization," *Bioorg Khim.*, 12(11):1508-1513 (1986).

Abbott et al., "Manipulation of the Wettability of Surfaces on the 0.1- to 1 -Micrometer Scale Through Micromachining and Molecular Self-Assembly," *Science*, 257:1380-1382 (1992).

Adams et al., "Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project," *Science*, 252(5013):1651-1656 (1991).

Adams et al., "Photolabile Chelators That "Cage" Calcium with Improved Speed of Release and Pre-Photolysis Affinity," *J. Gen. Physiol.*, p. 9a (12/86).

Adams et al., "Biologically Useful Chelators That Take Up Ca2+ upon Illumination," *J. Am. Chem. Soc.*, 111:7957-7968 (1989).

Ajayaghosh et al., "Solid-Phase Synthesis of N-Methyl- and N-Ethylamides of Peptides Using Photolytically Detachable ((3-Nitro-4((alkylamino)methyl)benzamido)methyl)polystyrene Resin," *J. Org. Chem.*, 55(9):2826-2829 (1990).

(List continued on next page.)

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(57) **ABSTRACT**

The present invention provides methods and apparatus for sequencing, fingerprinting and mapping biological macromolecules, typically biological polymers. The methods make use of a plurality of sequence specific recognition reagents which can also be used for classification of biological samples, and to characterize their sources.

22 Claims, 2 Drawing Sheets

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US 6,355,432 B1

Page 2

U.S. PATENT DOCUMENTS

| | | | | | | | |
|-------------|---------|--------------------|------------|-------------|---------|------------------------|-----------|
| 4,395,486 A | 7/1983 | Wilson et al. | 435/6 | 4,865,990 A | 9/1989 | Stead et al. | 435/803 |
| 4,405,771 A | 9/1983 | Jagur | 528/266 | 4,868,103 A | 9/1989 | Stavrianopoulos et al. | 435/5 |
| 4,444,878 A | 4/1984 | Paulus | 435/7 | 4,874,500 A | 10/1989 | Madou et al. | 204/412 |
| 4,444,892 A | 4/1984 | Malmros | 436/528 | 4,877,745 A | 10/1989 | Hayes et al. | 436/166 |
| 4,448,534 A | 5/1984 | Wertz et al. | 356/435 | 4,886,741 A | 12/1989 | Schwartz | 435/5 |
| 4,458,066 A | 7/1984 | Caruthers et al. | 536/27 | 4,888,278 A | 12/1989 | Singer et al. | 435/6 |
| 4,483,920 A | 11/1984 | Gillespie et al. | 435/6 | 4,921,805 A | 5/1990 | Gebeyehu et al. | 435/270 |
| 4,500,707 A | 2/1985 | Caruthers et al. | 536/27 | 4,923,901 A | 5/1990 | Koester et al. | 521/53 |
| 4,500,919 A | 2/1985 | Schreiber | 358/78 | 4,925,785 A | 5/1990 | Wang et al. | 435/6 |
| 4,516,833 A | 5/1985 | Fusek | 350/162.12 | 4,931,384 A | 6/1990 | Layton et al. | 435/7.31 |
| 4,517,338 A | 5/1985 | Urdea et al. | 525/54.11 | 4,946,942 A | 8/1990 | Fuller et al. | 530/335 |
| 4,533,682 A | 8/1985 | Tortorello et al. | 523/414 | 4,965,188 A | 10/1990 | Mullis et al. | 435/6 |
| 4,537,861 A | 8/1985 | Elings et al. | 436/518 | 4,973,493 A | 11/1990 | Guire | 427/2 |
| 4,542,102 A | 9/1985 | Dattagupta et al. | 435/6 | 4,979,959 A | 12/1990 | Guire | 623/66 |
| 4,555,490 A | 11/1985 | Merrill | 436/86 | 4,981,783 A | 1/1991 | Augenlicht | 435/6 |
| 4,556,643 A | 12/1985 | Pau et al. | 435/5 | 4,981,985 A | 1/1991 | Kaplan et al. | 556/50 |
| 4,562,157 A | 12/1985 | Lowe et al. | 435/291 | 4,984,100 A | 1/1991 | Takayama et al. | 360/49 |
| 4,563,419 A | 1/1986 | Ranki et al. | 435/6 | 4,987,065 A | 1/1991 | Stavrianopoulos et al. | 435/5 |
| 4,569,967 A | 2/1986 | Kornreich et al. | 525/54.11 | 4,988,617 A | 1/1991 | Landegren et al. | 435/6 |
| 4,580,895 A | 4/1986 | Patel | 356/39 | 4,992,383 A | 2/1991 | Farnsworth | 436/89 |
| 4,584,277 A | 4/1986 | Ullman | 436/501 | 4,994,373 A | 2/1991 | Stavrianopoulos et al. | 435/6 |
| 4,588,682 A | 5/1986 | Groet et al. | 435/6 | 5,002,867 A | 3/1991 | Macevicz | 435/6 |
| 4,591,570 A | 5/1986 | Chang | 435/7.24 | 5,006,464 A | 4/1991 | Chu et al. | 435/7.1 |
| 4,598,049 A | 7/1986 | Zelinka et al. | 422/116 | 5,011,770 A | 4/1991 | Kung et al. | 435/6 |
| 4,613,566 A | 9/1986 | Potter | 435/6 | 5,013,669 A | 5/1991 | Peters, Jr. et al. | 436/518 |
| 4,624,915 A | 11/1986 | Schindler et al. | 435/4 | 5,021,550 A | 6/1991 | Zieger | 530/334 |
| 4,626,684 A | 12/1986 | Landa | 250/328 | 5,026,773 A | 6/1991 | Steel | 525/54.11 |
| 4,631,211 A | 12/1986 | Houghten | 428/35 | 5,026,840 A | 6/1991 | Dattagupta et al. | 536/27 |
| 4,637,861 A | 1/1987 | Krull et al. | 204/1 T | 5,028,525 A | 7/1991 | Gray et al. | 435/6 |
| 4,656,127 A | 4/1987 | Mundy | 435/6 | 5,028,545 A | 7/1991 | Soini | 436/501 |
| 4,670,380 A | 6/1987 | Dattagupta | 435/6 | 5,037,882 A | 8/1991 | Steel | 525/54.11 |
| 4,677,054 A | 6/1987 | White et al. | 435/6 | 5,043,265 A | 8/1991 | Tanke et al. | 435/6 |
| 4,681,859 A | 7/1987 | Kramer | 436/501 | 5,047,524 A | 9/1991 | Andrus et al. | 536/27 |
| 4,683,195 A | 7/1987 | Mullis et al. | 435/6 | 5,064,754 A | 11/1991 | Mills | 435/6 |
| 4,683,202 A | 7/1987 | Mullis | 435/91 | 5,075,077 A | 12/1991 | Durley | |
| 4,689,405 A | 8/1987 | Frank et al. | 536/27 | 5,077,085 A | 12/1991 | Schnur et al. | 427/98 |
| 4,704,353 A | 11/1987 | Humphries et al. | 435/4 | 5,077,210 A | 12/1991 | Eigler et al. | 435/176 |
| 4,711,955 A | 12/1987 | Ward et al. | 536/29 | 5,079,600 A | 1/1992 | Schnur et al. | 357/4 |
| 4,713,326 A | 12/1987 | Dattagupta et al. | 435/6 | 5,081,584 A | 1/1992 | Omichinski et al. | 364/497 |
| 4,713,347 A | 12/1987 | Mitchell et al. | 436/501 | 5,082,830 A | 1/1992 | Brakel et al. | 514/44 |
| 4,715,413 A | 12/1987 | Backlund et al. | 141/94 | 5,091,652 A | 2/1992 | Mathies et al. | 250/458.1 |
| 4,716,106 A | 12/1987 | Chiswell | 435/6 | 5,096,807 A | 3/1992 | Leaback | 435/6 |
| 4,719,179 A | 1/1988 | Barany | 435/172.1 | 5,100,626 A | 3/1992 | Levin | 422/100 |
| 4,719,615 A | 1/1988 | Feyrer et al. | 369/284 | 5,100,777 A | 3/1992 | Chang | 435/7.24 |
| 4,722,906 A | 2/1988 | Guire | 436/501 | 5,112,962 A | 5/1992 | Letsinger et al. | 536/27 |
| 4,728,502 A | 3/1988 | Hamill | 422/116 | 5,141,813 A | 8/1992 | Nelson | 428/402 |
| 4,728,591 A | 3/1988 | Clark et al. | 430/5 | 5,143,854 A | 9/1992 | Pirung et al. | 436/518 |
| 4,731,325 A | 3/1988 | Palva et al. | 435/6 | 5,149,625 A | 9/1992 | Church et al. | 435/6 |
| 4,737,344 A | 4/1988 | Koizumi et al. | 422/100 | 5,153,319 A | 10/1992 | Caruthers et al. | 536/27 |
| 4,755,458 A | 7/1988 | Rabbani et al. | 435/5 | 5,164,319 A | 11/1992 | Hafeman et al. | 435/287.1 |
| 4,762,881 A | 8/1988 | Kauer | 525/54.11 | 5,171,695 A | 12/1992 | Ekins | 436/501 |
| 4,766,062 A | 8/1988 | Diamond et al. | 435/6 | 5,188,963 A | 2/1993 | Stapleton | 435/288.3 |
| 4,767,700 A | 8/1988 | Wallace | 435/6 | 5,192,980 A | 3/1993 | Dixon et al. | 356/326 |
| 4,777,019 A | 10/1988 | Dandekar | 422/68 | 5,200,051 A | 4/1993 | Cozzette et al. | 204/403 |
| 4,780,504 A | 10/1988 | Buendia et al. | 525/54.11 | 5,202,231 A | 4/1993 | Drmanac et al. | 435/6 |
| 4,786,170 A | 11/1988 | Groebler | 356/318 | 5,206,137 A | 4/1993 | Ip et al. | 435/6 |
| 4,786,684 A | 11/1988 | Glass | 525/54.1 | 5,215,882 A | 6/1993 | Bahl et al. | 435/6 |
| 4,794,150 A | 12/1988 | Steel | 525/54.11 | 5,215,889 A | 6/1993 | Schultz | 435/41 |
| 4,808,508 A | 2/1989 | Platzter | 430/143 | 5,219,726 A | 6/1993 | Evans | 435/6 |
| 4,810,869 A | 3/1989 | Yabe et al. | 250/201 | 5,225,326 A | 7/1993 | Bresser et al. | 435/6 |
| 4,811,062 A | 3/1989 | Tabata et al. | 356/152 | 5,232,829 A | 8/1993 | Longiaru et al. | 435/6 |
| 4,811,218 A | 3/1989 | Hunkapiller et al. | 204/461 | 5,235,028 A | 8/1993 | Barany et al. | 528/335 |
| 4,812,512 A | 3/1989 | Buendia et al. | 525/54.11 | 5,242,974 A | 9/1993 | Holmes | 525/54.11 |
| 4,820,630 A | 4/1989 | Taub | 435/5 | 5,252,743 A | 10/1993 | Barrett et al. | 548/303.7 |
| 4,822,566 A | 4/1989 | Newman | 422/68 | 5,256,549 A | 10/1993 | Urdea et al. | 435/91 |
| 4,833,092 A | 5/1989 | Geysen | 436/501 | 5,258,506 A | 11/1993 | Urdea et al. | 536/23.1 |
| 4,844,617 A | 7/1989 | Kelderman et al. | 356/372 | 5,306,641 A | 4/1994 | Saccocio | 436/85 |
| 4,846,552 A | 7/1989 | Veldkamp et al. | 350/162.2 | 5,310,893 A | 5/1994 | Erlich et al. | 536/24.31 |
| 4,849,513 A | 7/1989 | Smith et al. | 536/27 | 5,324,633 A | 6/1994 | Fodor et al. | 435/6 |
| 4,855,225 A | 8/1989 | Fung et al. | 435/6 | 5,328,824 A | 7/1994 | Ward et al. | 435/6 |
| | | | | 5,348,855 A | 9/1994 | Dattagupta et al. | 435/6 |

IAFP00000656

US 6,355,432 B1

Page 3

| | | | | | | |
|--------------------------|---------|------------------------|-----------|----|-------------|---------|
| 5,384,261 A | 1/1995 | Winkler et al. | 436/518 | EP | 307 476 | 3/1989 |
| 5,405,783 A | 4/1995 | Pirrung et al. | 436/518 | EP | 319 012 | 6/1989 |
| 5,424,186 A | 6/1995 | Fodor et al. | 435/6 | EP | 328 256 | 8/1989 |
| 5,424,188 A | 6/1995 | Schneider et al. | 435/6 | EP | 333 561 | 9/1989 |
| 5,432,099 A | 7/1995 | Ekins | 436/518 | EP | 337 498 | 10/1989 |
| 5,436,327 A | 7/1995 | Southern et al. | 536/25.34 | EP | 386 229 | 4/1990 |
| 5,445,934 A | 8/1995 | Fodor et al. | 435/6 | EP | 373 203 | 6/1990 |
| 5,447,841 A | 9/1995 | Gray et al. | 435/6 | EP | 392 546 | 10/1990 |
| 5,451,505 A | 9/1995 | Dollinger | | EP | 142 299 | 12/1990 |
| 5,474,796 A | 12/1995 | Brennan | 427/2.13 | EP | 173 339 | 1/1992 |
| 5,486,452 A | 1/1996 | Gordon et al. | 435/5 | EP | 171 150 | 3/1992 |
| 5,489,507 A | 2/1996 | Chehab | 435/6 | EP | 237 362 | 3/1992 |
| 5,489,678 A | 2/1996 | Fodor et al. | 536/22.1 | EP | 185 547 | 6/1992 |
| 5,492,806 A | 2/1996 | Drmanac et al. | 435/5 | EP | 260 634 | 6/1992 |
| 5,494,810 A | 2/1996 | Barany et al. | 435/91.52 | EP | 232 967 | 4/1993 |
| 5,510,270 A | 4/1996 | Fodor et al. | 436/518 | EP | 235 726 | 5/1993 |
| 5,525,464 A | 6/1996 | Drmanac et al. | 435/6 | EP | 476 014 | 8/1994 |
| 5,527,681 A | 6/1996 | Holmes | 435/6 | EP | 225 807 | 10/1994 |
| 5,552,270 A | 9/1996 | Khrapko et al. | 435/6 | EP | 717 113 | 6/1996 |
| 5,556,961 A | 9/1996 | Foot et al. | 536/27.1 | EP | 721 016 | 7/1996 |
| 5,561,071 A | 10/1996 | Hollenberg et al. | 437/1 | EP | 535 242 | 9/1997 |
| 5,565,324 A | 10/1996 | Still | | EP | 848 067 | 6/1998 |
| 5,567,809 A | 10/1996 | Mandecki | | EP | 619 321 | 1/1999 |
| 5,569,584 A | 10/1996 | Augenlicht | 435/6 | FR | 2559783 | 3/1988 |
| 5,571,639 A | 11/1996 | Hubbell et al. | 430/5 | GB | 2 129 551 | 5/1984 |
| 5,573,905 A | 11/1996 | Lerner | | GB | 2156074 | 3/1988 |
| 5,593,839 A | 1/1997 | Hubbell et al. | 435/6 | GB | 2196476 | 4/1988 |
| 5,599,720 A | 2/1997 | Ekins | 436/501 | GB | 8810400.5 | 5/1988 |
| 5,604,097 A | 2/1997 | Brenner | | GB | 2233654 | 1/1991 |
| 5,604,099 A | 2/1997 | Erlich et al. | 435/6 | GB | 2248840 | 9/1992 |
| 5,635,400 A | 6/1997 | Brenner | | JP | 49-110601 | 10/1974 |
| 5,641,634 A | 6/1997 | Mandecki | | JP | 60-248669 | 12/1985 |
| 5,643,728 A | 7/1997 | Slater et al. | 435/6 | JP | 63-084499 | 4/1988 |
| 5,653,939 A | 8/1997 | Hollis et al. | 422/50 | JP | 63-223557 | 9/1988 |
| 5,654,413 A | 8/1997 | Brenner | | JP | 1-233447 | 9/1989 |
| 5,667,667 A | 9/1997 | Southern | 205/687 | NO | P 913186 | 8/1991 |
| 5,667,972 A | 9/1997 | Drmanac et al. | 435/6 | WO | WO 84/03151 | 8/1984 |
| 5,690,894 A | 11/1997 | Pinkel | | WO | WO 84/03564 | 9/1984 |
| 5,695,940 A | 12/1997 | Drmanac et al. | 435/6 | WO | WO 85/01051 | 3/1985 |
| 5,698,393 A | 12/1997 | Macioszek et al. | 435/5 | WO | WO 86/00991 | 2/1986 |
| 5,700,637 A | 12/1997 | Southern | 435/6 | WO | WO 86/06487 | 11/1986 |
| 5,707,806 A | 1/1998 | Shuber | | WO | WO 88/01058 | 2/1988 |
| 5,744,305 A | 4/1998 | Fodor et al. | 435/6 | WO | WO 88/04777 | 6/1988 |
| 5,751,629 A | 5/1998 | Nova | | WO | WO 89/05616 | 6/1989 |
| 5,770,367 A | 6/1998 | Southern | | WO | WO 89/08834 | 9/1989 |
| 5,776,737 A | 7/1998 | Dunn | 435/91.1 | WO | WO 89/10977 | 11/1989 |
| 5,777,888 A | 7/1998 | Rine et al. | 364/496 | WO | WO 89/11548 | 11/1989 |
| 5,800,992 A | 9/1998 | Fodor et al. | 435/6 | WO | WO 89/12819 | 12/1989 |
| 5,804,563 A | 9/1998 | Still | | WO | WO 90/00626 | 1/1990 |
| 5,807,522 A | 9/1998 | Brown | | WO | WO 90/00887 | 2/1990 |
| 5,807,683 A | 9/1998 | Brenner | | WO | WO 90/15070 | 2/1990 |
| 5,830,645 A | 11/1998 | Pinkel et al. | 435/6 | WO | WO 90/03382 | 4/1990 |
| 5,843,767 A | 12/1998 | Beattie | 435/287.1 | WO | WO 90/04652 | 5/1990 |
| 5,846,708 A | 12/1998 | Hollis et al. | 435/6 | WO | WO 90/05789 | 5/1990 |
| 5,846,719 A | 12/1998 | Brenner | | WO | WO 90/07582 | 7/1990 |
| 5,863,722 A | 1/1999 | Brenner | | WO | WO 91/00868 | 1/1991 |
| 5,869,237 A | 2/1999 | Ward et al. | 435/6 | WO | WO 91/04266 | 4/1991 |
| 5,871,697 A | 2/1999 | Rothberg et al. | 422/68.1 | WO | WO 91/07087 | 5/1991 |
| 5,972,619 A | 10/1999 | Drmanac et al. | 435/6 | WO | WO 92/16655 | 1/1992 |
| 6,018,041 A | 1/2000 | Drmanac et al. | 536/24.3 | WO | WO 92/10092 | 6/1992 |
| 6,023,540 A | 2/2000 | Walt | | WO | WO 92/10588 | 6/1992 |
| 6,025,136 A | 2/2000 | Drmanac et al. | 435/6 | WO | WO 93/02992 | 2/1993 |
| 6,040,166 A | 3/2000 | Erlich et al. | 435/194 | WO | WO 93/09668 | 5/1993 |
| 6,054,270 A | 4/2000 | Southern | 435/6 | WO | WO 88/01302 | 6/1993 |
| 6,060,240 A | 5/2000 | Kamb | | WO | WO 93/11262 | 6/1993 |
| FOREIGN PATENT DOCUMENTS | | | | WO | WO 93/17126 | 9/1993 |
| EP | 281 927 | 9/1988 | | WO | WO 93/22456 | 11/1993 |
| EP | 228 310 | 10/1988 | | WO | WO 93/22480 | 11/1993 |
| EP | 288 310 | 10/1988 | | WO | WO 95/00530 | 1/1995 |
| EP | 304 202 | 2/1989 | | WO | WO 95/11995 | 5/1995 |
| | | | | WO | WO 95/33846 | 12/1995 |

IAFP00000657

US 6,355,432 B1

Page 4

| | | |
|----|-------------|---------|
| WO | WO 96/23078 | 8/1996 |
| WO | WO 97/10365 | 3/1997 |
| WO | WO 97/17317 | 5/1997 |
| WO | WO 97/19410 | 5/1997 |
| WO | WO 97/27317 | 7/1997 |
| WO | WO 97/29212 | 8/1997 |
| WO | WO 97/31256 | 8/1997 |
| WO | WO 97/45559 | 12/1997 |
| WO | WO 98/03673 | 1/1998 |
| WO | WO 98/31836 | 7/1998 |
| WO | WO 99/60007 | 11/1999 |
| YU | P-570/87 | 4/1987 |
| YU | 18617/87 | 9/1987 |

OTHER PUBLICATIONS

- Ajayaghosh et al., "Solid-phase synthesis of C-terminal peptide amides using a photoremovable α -methoxyphenacylamido anchoring linkage," *Proc. Ind. Natl. Sci. (Chem. Sci.)*, 100(5):389-396 (1988).
- Ajayaghosh et al., "Polymer-supported Solid-phase Synthesis of C-Terminal Peptide N-Methylamides Using a Modified Photoremovable 3-Nitro-4-N-methylaminomethylpolystyrene Support," *Ind. J. Chem.*, 27B:1004-1008 (1988).
- Ajayaghosh et al., "Polymer-Supported Synthesis of Protected Peptide Segments on a Photosensitive o-Nitro (α -Methyl)Bromobenzyl Resin," *Tetrahedron*, 44(21):6661-6666 (1988).
- Amit et al., "Photosensitive Protecting Groups of Amino Sugars and Their Use in Glycoside Synthesis. 2-Nitrobenzyloxycarbonylamino and 6-Nitroveratryloxycarbonylamino Derivatives," *J. Org. Chem.*, 39(2):192-196 (1974).
- Amit et al., "Photosensitive Protecting Groups—A Review," *Israel J. Chem.*, 12(1-2):103-113 (1974).
- Anand et al., "A 3.5 genome equivalent multi access YAC library: construction, characterisation, screening and storage," *Nuc. Acids Res.*, 18(8):1951-1956 (1990).
- Anderson et al., "Quantitative Filter Hybridisation," chapter 3 from *Nucleic Acid Hybridization a practical approach*, pp. 73-111, Hames et al., eds., IRL Press (1985).
- Applied Biosystems, Model 431A Peptide Synthesizer User's manual, Sections 2 and 6, (Aug. 15, 1989).
- Anold et al., "A Novel Universal Support for DNA & RNA Synthesis," abstract from *Federation Proceedings*, 43(7):abstract No. 3669 (1984).
- Atherton et al., *Solid Phase Peptide Synthesis: A Practical Approach*, IRL Press, (1989), tbl. of cont., pp. vii-ix.
- Augenlicht et al., "Cloning and Screening of Sequences Expressed in a Mouse Colon Tumor," *Cancer Research*, 42:1088-1093 (1982).
- Augenlicht et al., "Expression of Cloned Sequences in Biopsies of Human Colonic Tissue and in Colonic Carcinoma Cells Induced to Differentiate in Vitro," *Cancer Res.*, 47:6017-6021 (1987).
- Bains, W., "Hybridization Methods for DNA Sequencing," *Genomics*, 11(2):294-301 (1991).
- Bains et al., "A Novel Method for Nucleic Acid Sequence Determination," *J. Theor. Biol.*, 135:303-307 (1988).
- Bains, W., "Alternative Routes Through the Genome," *Biotechnology*, 8:1251-1256 (1988).
- Balachander et al., "Functionalized Siloxy-Anchored Monolayers with Exposed Amino, Azido, Bromo, or Cyano Groups," *Tetrahed. Ltrs.*, 29(44):5593-5594 (1988).
- Baldwin et al., "New Photolabile Phosphate Protecting Groups," *Tetrahed.*, 46(19):6879-6884 (1990).
- Bannwarth et al., "Laboratory Methods, A System for the Simultaneous Chemical synthesis of Different DNA Fragments on Solid Support," *DNA*, 5(5):413-419 (1986).
- Bannwarth, W., "Gene Technology: a Challenge for a Chemist," *Chimia*, 41(9):302-317 (1987).
- Barany, F., "Genetic disease detection and DNA amplification using cloned thermostable ligase," *PNAS*, 88:189-193 (1991).
- Bartrop et al., "Photosensitive Protective Groups," *Chemical Communications*, pp. 822-823 (1966).
- Barinaga, M., "Will 'DNA Chip' Speed Genome Initiative," *Science*, 253:1489 (1985).
- Bart et al., "Microfabricated Electrohydrodynamic Pumps," *Sensors and Actuators*, A21:-A23:193-197 (1990).
- Bartsh et al., "Cloning of mRNA sequences from the human colon: Preliminary characterisation of defined mRNAs in normal and neoplastic tissues," *Br. J. Can.*, 54:791-798 (1986).
- Baum, R., "Fledgling firm targets drug discovery process," *Chem. Eng. News*, p. 10-11 (1990).
- Beltz et al., "Isolation of Multigene Families and Determination of Homologies by Filter Hybridization Methods," *Methods in Enzymology*, 100:266-285 (1983).
- Benschop, Chem. Abstracts 114(26):256643 (1991).
- Bhatia et al., "New Approach To Producing Patterned Biomolecular Assemblies," *J. American Chemical Society*, 114:4432-4433 (1992).
- Biorad Chromatography Electrophoresis Immunochemistry Molecular Biology HPLC catalog M 1987 pp. 182.
- Blawas et al., "Step-and-Repeat Photopatterning of Protein Features Using Caged-Biotin-BSA: Characterization and Resolution," *Langmuir*, 14(15):4243-4250 (1998).
- Blawas, A.S., "Photopatterning of Protein Features using Caged-biotin-Bovine Serum Albumin," dissertation for Ph.D at Duke University in 1998.
- Bos et al., "Amino-acid substitutions at codon 13 of the N-ras oncogene in human acute myeloid leukaemia," *Nature*, 315:726-730 (1985).
- Boyle et al., "Differential distribution of long and short interspersed element sequences in the mouse genome: Chromosome karyotyping by fluorescence in situ hybridization," *PNAS*, 87:7757-7761 (1990).
- Brock et al., "Rapid fluorescence detection of in situ hybridization with biotinylated bovine herpesvirus-1 DNA probes," *J. Veterinary Diagnostic Invest.*, 1:34-38 (1989).
- Burgi et al., "Optimization in Sample Stacking for High-Performance Capillary Electrophoresis," *Anal. Chem.*, 63:2042-2047 (1991).
- Cameron et al., "Photogeneration of Organic Bases from o-Nitrobenzyl-Derived Carbamates," *J. Am. Chem. Soc.*, 113:4303-4313 (1991).
- Carrano et al., "A High-Resolution, Fluorescence-Based, Semiautomated Method for DNA Fingerprinting," *Genomics*, 4:129-136 (1989).
- Caruthers, M.H., "Gene Synthesis Machines: DNA Chemistry and Its Uses," *Science*, 230:281-285 (1985).
- Chatterjee et al., "Inducible Alkylation of DNA Using an Oligonucleotide-Quinone Conjugates," *Am. J. Chem. Soc.*, 112:6397-6399 (1990).
- Chee et al., "Accessing Genetic Information with High-Density DNA Arrays," *Science*, 274:610-614 (1996).
- Chehab et al., "Detection of sickle cell anaemia mutation by colour DNA amplification," *Lancet*, 335:15-17 (1990).

IAFP00000658

US 6,355,432 B1

Page 5

- Chehab et al., "Detection of specific DNA sequences by fluorescence amplification: A color complementation assay," *PNAS*, 86:9178-9182 (1989).
- Chetverin et al., "Oligonucleotide Arrays: New Concepts and Possibilities," *Biotechnology*, 12:1093-1099 (1994).
- Church et al., "Multiplex DNA sequencing," *Science*, 240:185-188 (1988).
- Church et al., "Genomic sequencing," *PNAS*, 81:1991-1995 (1984).
- Clevite Corp., Piezoelectric Technology, Data for Engineers.
- Corbett et al., "Reaction of Nitroso Aromatics with Glyoxylic Acid. A New Path to Hydroxamic Acids," *J. Org. Chem.*, 45:2834-2839 (1980).
- Coulson et al., "Toward a physical map of the genome of the nematode *Caenorhabditis elegans*," *PNAS*, 83:7821-7825 (1986).
- Craig et al., "Ordering of cosmid clones covering the Herpes simplex virus type 1 (HSV-1) genome: a test case for fingerprinting the hybridization," *Nuc. Acid. Res.*, 18(9):2653-2660 (1990).
- Cummings et al., "Photoactivable Fluorophores. 1. Synthesis and Photoactivation of o-Nitrobenzyl-Quenched Fluorescent Carbamates," *Tetrahedron Letters*, 29(1):65-68 (1988).
- Dattagupta et al., "Rapid identification of Microorganisms by Nucleic Acid Hybridization after Labeling the Test Sample," *Anal. Biochem.*, 177:85-89 (1989).
- Dattagupta et al., "Nucleic Acid Hybridization: a Rapid Method for the Diagnosis of Infectious Diseases," *Perspectives in Antiinfective Therapy*, eds. Jackson et al., pp. 241-247 (1988).
- Dower et al., "The Search for Molecular Diversity (II): Recombinant and Synthetic Randomized Peptide Libraries," *Ann. Rep. Med. Chem.*, 26:271-280 (1991).
- Diggelmann, "Investigating the VLSIPS synthesis process," Sep. 9, 1994.
- Di Mauro et al., "DNA Technology in Chip Construction," *Adv. Mater.*, 5(5):384-386 (1993).
- Drmanac et al., "An Algorithm for the DNA Sequence Generation from k-Tuple Word Contents of the Minimal Number of Random Fragments," *J. Biomol. Struct. Dyn.*, 8(5):1085-1102 (1991).
- Drmanac et al., "Partial Sequencing by Oligo-Hybridization Concept and Applications in Genome Analysis," 1st Int. Conf. Electrophor., Supercomp., Hum. Genome pp. 60-74 (1990).
- Drmanac et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?," 1st Int. Conf. Electrophor., Supercomp., Hum. Genome pp. 47-59 (1990).
- Drmanac et al., "Laboratory Methods, Reliable Hybridization: theory of the Method," *Genomics*, 4:114-128 (1989).
- Drmanac et al., "Sequencing of Megabase Plus DNA by Hybridization: Theory of the Method," abstract of presentation given at Cold Spring Harbor Symposium on Genome Mapping and Sequencing, Apr. 27, 1988 thru May 1, 1988.
- Dulcey et al., "Deep UV Photochemistry of Chemisorbed Monolayers: Patterned Coplanar Molecular Assemblies," *Science*, 252:551-554 (1991).
- Duncan et al., "Affinity Chromatography of a Sequence-Specific DNA Binding Protein Using Teflon-Linked Oligonucleotides," *Analytical Biochemistry*, 169:104-108 (1988).
- Effenhauser et al., "Glass Chips for High-speed Capillary Electrophoresis Separations with Submicrometer Plate Heights," *Anal. Chem.*, 65:2637-2642 (1993).
- Effenhauser et al., "High-Speed Separation of Antisense Oligonucleotides on a Micromachined Capillary Electrophoresis Device," *Anal. Chem.*, 66:2949-2953 (1994).
- Ekins et al., "High Specific Activity Chemiluminescent and Fluorescent Markers: their Potential Application to High Sensitivity and 'Multi-analyte' Immunoassays," *J. Bioluminescence Chemiluminescence*, 4:59-78 (1989).
- Ekins et al., "Development of Microspot Multi-Analyte Radiometric Immunoassay Using dual Fluorescent-Labelled Antibodies," *Anal. Chimica Acta*, 227:73-96 (1989).
- Ekins et al., "Multianalyte Microspot Immunoassay-Microanalytical 'Compact Disk' of the Future," *Clin. Chem.*, 37(11):1955-1967 (1991).
- Ekins, R.P., "Multi-Analyte immunoassay*," *J. Pharmaceutical Biomedical Analysis*, 7(2):155-168 (1989).
- Ekins et al., "Fluorescence Spectroscopy and its Application to a New Generation of High Sensitivity, Multi-Microspot, Multianalyte, Immunoassay," *Clin. Chim. Acta*, 194:91-114 (1990).
- Elder, J.K., "Analysis of DNA Oligonucleotide Hybridization Data by Maximum Entropy," *Maximum Entropy and Bayesian Methods*, eds. Mohammad-Djafari and Dement, Kluwer, Dordrecht, pp. 363-371 (1992).
- Ellis, R.W., "The Applications of Synthetic Oligonucleotides to Molecular Biology," *Pharmaceutical Research*, 3(4):195-207 (1986).
- Evans et al., "Microfabrication for Automation of Molecular processes in Human Genome Analysis," *Clin. Chem.*, 41(11):1681 (1995).
- Evans et al., "Physical mapping of complex genomes by cosmid multiplex analysis," *PNAS*, 86:5030-5034 (1989).
- Ezaki et al., "Small-Scale DNA Preparation for Rapid Genetic Identification of *Campylobacter* Species without Radioisotope," *Microbiol. Immunology*, 32(2):141-150 (1988).
- Fan et al., "Mapping small DNA sequences by fluorescence in situ hybridization directly on banded metaphase chromosomes," *PNAS*, 87(16):6223-6227 (1990).
- Fan et al., "Micromachining of Capillary Electrophoresis Injectors and Separators on Glass Chips and Evaluation of Flow at Capillary Intersections," *Anal. Chem.*, 66:177-184 (1994).
- Feinberg et al., Addendum to "A technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity," *Anal. Biochem.*, 137:266-267 (1984).
- Fettingner et al., "Stacked modules for micro flow systems in chemical analysis: concept and studies using an enlarged model," *Sensors and Actuators*, B17:19-25 (1993).
- Flanders et al., "A new interferometric alignment technique," *App. Phys. Lett.*, 31(7):426-429 (1977).
- Fodor et al., "Multiplexed biochemical assays with biological chips," *Nature*, 364:555-556 (1993).
- Fodor et al., "Light-directed, Spatially Addressable Parallel Chemical Synthesis," *Science*, 251:767-773 (1991).
- Forman et al., "Thermodynamics of Duplex Formation and Mismatch Discrimination on Photolithographically Synthesized Oligonucleotide Arrays," chapter 13pgs. 206-228 from *Molecular Modeling of Nucleic Acids*, ACS Symposium Series 682, 4/13-17/97, Leontis et al., eds.

IAFP00000659

US 6,355,432 B1

Page 6

- Frank et al., "Simultaneous Multiple Peptide Synthesis Under Continuous flow Conditions on Cellulose Paper Discs as Segmental Solid Supports," *Tetrahedron*, 44(19):6031-6040 (1988).
- Frank et al., "Automation of DNA Sequencing Reactions and Related Techniques: A Workstation for Micromanipulation of Liquids," *Bio/Technology*, 6:1211-1212 (1988).
- Frank et al., "Simultaneous Synthesis and Biological Applications of DNA Fragments: An Efficient and Complete Methodology," *Methods in Enzymology*, 154:221-250 (1987).
- Fuhr et al., "Travelling wave-driven microfabricated electrohydrodynamic pumps for liquids," *J. Micromech. Microeng.*, 4:217-226 (1994).
- Fuller et al., "Urethane-Protected Amino Acid N-Carboxy Anhydrides and Their Use in Peptide Synthesis," *J. Amer. Chem. Soc.*, 112(20):7414-7416 (1990).
- Furka et al., "General method for rapid synthesis of multi-component peptide mixtures," *Int. J. Peptide Protein Res.*, 37:487-493 (1991).
- Furka et al., "Cornucopia of Peptides by Synthesis," 14th Int. Congress of Biochem. abst.# FR:013, 7/10-15/88 Prague, Czechoslovakia.
- Furka et al., "More Peptides by Less Labour," abst. 288, Int. Symp. Med. Chem., Budapest Hungary.
- Gait, eds., pp. 1-115 from *Oligonucleotide Synthesis: A Practical Approach*, IRL Press, (1984).
- Gazard et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid into Poly(Methyl Methacrylate) Films," *Polymer Engineering and Science*, 20(16):1069-1072 (1980).
- Gergen et al., "Filter replicas and permanent collections of recombinant DNA plasmids," *Nuc. Acids Res.*, 7(8):2115-2137 (1979).
- Getzoff et al., "Mechanisms of Antibody Binding to a Protein," *Science*, 235:1191-1196 (1987).
- Geysen et al., "Strategies for epitope analysis using peptide synthesis," *J. Immunol. Meth.*, 102:259-274 (1987).
- Geysen et al., "Use of peptide synthesis to probe viral antigens for epitopes to a resolution of a single amino acid," *PNAS*, 81:3998-4002 (1984).
- Geysen et al., "A synthetic strategy for epitope mapping," from *Peptides: Chem. & Biol.*, Proc. of 10th Am. Peptide Symp., 5/23-28/87, pp. 519-523, (1987).
- Geysen, "Antigen-antibody interactions at the molecular level: adventures in peptide synthesis," *Immunol. Today*, 6(12):364-369 (1985).
- Geysen et al., "Cognitive Features of Continuous Antigenic Determinants," from *Synthetic Peptides: Approaches to Biological Probes*, pp. 19-30, (1989).
- Geysen et al., "Chemistry of Antibody Binding to a Protein," *Science*, 235:1184-1190 (1987).
- Geysen et al., "The delineation of peptides able to mimic assembled epitopes," 1986 CIBA Symp., pp. 130-149.
- Geysen et al., "Cognitive Features of Continuous Antigenic Determinants," *Mol. Recognit.*, 1(1):1-10 (1988).
- Geysen et al., "A Prio Ri Delineation of a Peptide Which Mimics A Discontinuous Antigenic Determinant," *Mol. Immunol.*, 23(7):709-715 (1986).
- Ghosh et al., "Covalent attachment of oligonucleotides to solid supports," *Nuc. Acids Res.*, 15(13):5353-5373 (1987).
- Gilon et al., "Backbone Cyclization: A New Method for Conferring Conformational Constraint on Peptides," *Biopolymers*, 31(6):745-750 (1991).
- Gingeras et al., "Hybridization properties of immobilized nucleic acids," *Nuc. Acids Res.*, 15(13):5373-5390 (87).
- Gummerlock et al., "RAS Enzyme-Linked Immunoblot Assay Discriminates p21 Species: A Technique to Dissect Gene Family Expression," *Anal. Biochem.*, 180:158-168 (1989).
- Gurney et al., "Activation of a potassium current by rapid photochemically generated step increases of intracellular calcium in rat sympathetic neurons," *PNAS*, 84:3496-3500 (1987).
- Haase et al., "Detection of Two Viral Genomes in Single Cells by Double-Label Hybridization in Situ and Color Microradioautography," *Science*, 227:189-192 (1985).
- Hacia, et al., "Two color hybridization analysis using high density oligonucleotide arrays and energy transfer dyes," *Nuc. Acids Res.*, 26(16):3865-3866 (1998).
- Hack, M.L., "Conics Formed to Make Fluid & Industrial Gas Micromachines," *Genetic Engineering News*, 15(18):1, 29 (1995).
- Hagedorn et al., "Pumping of Water Solutions in Microfabricated Electrohydrodynamic Systems," from Micro Electro Mechanical Systems conference in Travemunde Germany (1992).
- Hames et al., *Nuclear acid hybridization, a practical approach*, cover page and table of contents (1985).
- Hanahan et al., "Plasmid Screening at High Colony Density," *Meth. Enzymology*, 100:333-342 (1983).
- Hanahan et al., "Plasmid screening at high colony density," *Gene*, 10:63-67 (1980).
- Haridasan et al., "Peptide Synthesis using Photolytically Cleavable 2-Nitrobenzyloxycarbonyl Protecting Group," *Proc. Indian Natn. Sci. Acad.*, 53A(6):717-728 (1987).
- Harrison et al., "Capillary Electrophoresis and Sample Injection Systems Integrated on a Planar Glass Chip," *Anal. Chem.*, 64:1926-1932 (1992).
- Harrison et al., "Micromachining a Minaturized Capillary Electrophoresis-Based Chemical Analysis System on a Chip," *Science*, 261:895-897 (1993).
- Harrison et al., "Towards minaturized electrophoresis and chemical analysis systems on silicon: an alternative to chemical sensors*," *Sensors and Actuators*, B10:107-116 (1993).
- Harrison et al., "Rapid separation of fluorescein derivatives using a micromachined capillary electrophoresis system," *Analytica Chimica Acta*, 283:361-366 (1993).
- Hellberg et al., "Minimum analogue peptide sets (MAPS) for quantitative structure-activity relationships," *Int. J. Peptide Protein Res.*, 37:414-424 (1991).
- Hilser et al., "Protein and peptide mobility in capillary zone electrophoresis, A comparison of existing models and further analysis," *J. Chromatography*, 630:329-336 (1993).
- Ho et al., "Highly Stable Biosensor Using an Artificial Enzyme," *Anal. Chem.*, 59:536-537 (1987).
- Hochgeschwender et al., "Preferential expression of a defined T-cell receptor β -chain gene in hapten-specific cytotoxic T-cell clones," *Nature*, 322:376-378 (1986).
- Hodgson, J., "Assays A La Photolithography," *Biotech.*, 9:419 (1991).
- Hodgson et al., "Hybridization probe size control: optimized 'oligolabelling'," *Nuc. Acids Res.*, 15(15):6295 (1987).
- Hopman et al., "Bi-color detection of two target DNAs by non-radioactive in situ hybridization*," *Histochem.*, 85:1-4 (1986).

IAFP00000660

US 6,355,432 B1

Page 7

- Iwamura et al., "1-Pyrenylmethyl Esters, Photolabile Protecting Groups for Carboxylic Acids," *Tetrahedron Lett.*, 28(6):679-682 (1987).
- Iwamura et al., "1-(α -Diazobenzyl)pyrene: A Reagent for Photolabile and Fluorescent Protection of Carboxyl Groups of Amino Acids and Peptides," *Synlett*, p. 35-36 (1991).
- Jacobson et al., "Effects of Injection Schemes and Column Geometry on the Performance of Microchip Electrophoresis Devices," *Anal. Chem.*, 66:1107-1113 (1994).
- Jacobsen et al., "Open Channel Electrochromatography on a Microchip," *Anal. Chem.*, 66:2369-2373 (1994).
- Jacobson et al., "Microchip Capillary Electrophoresis with an Integrated Postcolumn Reactor" *Anal. Chem.*, 66:3472-3476 (1994).
- Jacobson et al., "Precolumn Reactions with Electrophoretic Analysis Integrated on a Microchip," *Anal. Chem.*, 66:4127-4132 (1994).
- Jacobson et al., "Microfabricated chemical measurement systems," *Nature Medicine*, 1(10):1093-1096 (1995).
- Jacobsen et al., "Fused Quartz Substrates for Microchip Electrophoresis," *Anal. Chem.*, 67:2059-2063 (1995).
- Jacobson et al., "High-Speed Separations on a Microchip," *Anal. Chem.*, 66:1114-1118 (1994).
- Jacobson et al., "Microchip electrophoresis with sample stacking," *Electrophoresis*, 16:481-486 (1995).
- Jayakumar, "Peptide synthesis in a triphasic medium catalysed by papain immobilized on a crosslinked polystyrene support," *Indian J. Chemistry*, 29B:514-517 (1990).
- Jovin et al., "Luminescence Digital Imaging Microscopy," *Ann. Rev. Biophys. Biophys. Chem.*, 18:271-308 (1989).
- Kafatos et al., "Determination of nucleic acid sequence homologies and relative concentrations by a dot hybridization procedure," *Nuc. Acids Res.*, 7(6):1541-1553 (1979).
- Kaiser et al., "Peptide and Protein Synthesis by Segment Synthesis-Condensation," *Science*, 243:187-192 (1989).
- Kaplan et al., "Photolabile chelators for the rapid photorelease of divalent cations," *PNAS*, 85:6571-6575 (1988).
- Karube, "Micro-biosensors based on silicon fabrication technology," chapter 25 from *Biosensors: Fundamentals and Applications*, Turner et al., eds., Oxford Publ., 1987, pp. 471-480 (1987).
- Kates et al., "A Novel, Convenient, Three-dimensional Orthogonal Strategy for Solid-Phase Synthesis of Cyclic Peptides 1-3," *Tetrahed. Letters*, 34(10):1549-1552 (1993).
- Kerkof et al., "A Procedure for Making Simultaneous Determinations of the Relative Levels of Gene Transcripts in Tissues or Cells," *Anal. Biochem.*, 188:349-355 (1990).
- Khrapko et al., "An Oligonucleotide hybridization approach to DNA sequencing," *FEBS Lett.*, 256(1,2):118-122 (1989).
- Khrapko et al., "A method for DNA sequencing by hybridization with oligonucleotide matrix," *DNA Seq. Map.*, 1:375-388 (1991).
- Kidd et al., " α_1 -Antitrypsin deficiency detection by direct analysis of the mutation in the gene," *Nature*, 304:230-234 (1983).
- Kievits et al., "Rapid subchromosomal localization of cosmids by nonradioactive in situ hybridization," *Cytogenetics Cell Genetics*, 53(2-3):134-136 (1990).
- Kimura et al., "An Immobilized Enzyme Membrane Fabrication Method using an Ink Jet Nozzle," *Biosensors*, 4:41-52 (1988).
- Kimura et al., "An Integrated SOS/FET Multi-Biosensor," *Sensors & Actuators*, 9:373-387 (1986).
- Kitazawa et al., "In situ DNA-RNA hybridization using in vivo bromodeoxyuridine-labeled DNA probe," *Histochemistry*, 92:195-199 (1989).
- Kleinfeld et al., "Controlled Outgrowth of Dissociated Neurons on Patterned Substrates," *J. Neurosci.*, 8(11):4098-4120 (1988).
- Knight, P., "Materials and Methods/Microsequencers for Proteins and Oligosaccharides," *Bio/Techn.*, 7:1075-76 (1989).
- Kohara et al., "The Physical Map of the Whole *E. coli* Chromosome: Application of a New Strategy for Rapid Analysis and Sorting of a Large Genomic Library," *Cell*, 50:495-508 (1987).
- Krile et al., "Multiplex holography with chirp-modulated binary phase-coded reference-beam masks," *Applied Opt.*, 18(1):52-56 (1979).
- Labat, I., "Subfragments as an informative characteristic of the DNA molecule—computer simulation," research report submitted to the University of Belgrade College of Natural Sciences and Mathematics, (1988).
- Lander et al., "Genomic Mapping by Fingerprinting Random Clones: A Mathematical Analysis," *Genomics*, 2:231-239 (1988).
- Lainer et al., "Human Lymphocyte Subpopulations Identified by Using Three-Color Immunofluorescence and Flow Cytometry Analysis: Correlation of Leu-2, Leu-3, Leu-7, Leu-8, and Leu-11 Cell Surface Antigen Expression," *Journal of Immunology*, 132(1):151-156 (1984).
- Lam et al., "A new type of synthetic peptide library for identifying ligand-binding activity," *Nature*, 354:82-84 (1991).
- Laskey et al., "Messenger RNA prevalence in sea urchin embryos measured with cloned cDNAs," *PNAS*, 77(9):5317-5321 (1980).
- Lee et al., "synthesis of a Polymer Surface Containing Covalently Attached Triethoxysilane Functionality: Adhesion to Glass," *Macromolecules*, 21:3353-3356 (1988).
- Lebrach et al., "Labelling oligonucleotides to high specific activity (I)," *Nuc. Acids Res.*, 17(12):4605-4610 (89).
- Lehrach et al., "Phage Vectors—EMBL Series," *Meth. Enzymology*, 153:103-115 (1987).
- Lehrach et al., "Hybridization Fingerprinting in Genome Mapping and Sequencing," *Genome Analysis vol. 1: Genetic and Physical Mapping*, Cold Spring Harbor Laboratory Press, pp. 39-81 (1990).
- Levy, M.F., "Preparing Additive Printed Circuits," *IBM Tech. Discl. Bull.*, 9(11):1473 (1967).
- Lewin, Benjamin, eds., *Genes*, third edition, John Wiley & Sons, cover page, preface and table of contents, (1987).
- Lichter et al., "High-Resolution Mapping of Human Chromosome 11 by in Situ hybridization with Cosmid Clones," *Science*, 247:64-69 (1990).
- Lichter et al., "Fluorescence in situ hybridization with Alu and L1 polymerase chain reaction probes for rapid characterization of human chromosomes in hybrid cell lines," *PNAS*, 87:6634-6638 (1990).
- Lichter et al., "Rapid detection of human chromosome 21 aberrations by in situ hybridization," *PNAS*, 85:9664-9668 (1988).
- Lichter et al., "Is non-isotopic in situ hybridization finally coming of age," *Nature*, 345:93-94 (1990).
- Lieberman et al., "A Light source Smaller Than the Optical Wavelength," *Science*, 247:59-61 (1990).

US 6,355,432 B1

Page 8

- Lipshutz et al., "Using Oligonucleotide Probe Arrays To Access Genetic Diversity," *BioTech.*, 19(3):442-7 (1995).
- Little, P., "Clone maps made simple," *Nature*, 346:611-612 (1990).
- Liu et al., "Sequential Injection Analysis in Capillary Format with an Electroosmotic Pump," *Talanta*, 41(11):1903-1910 (1994).
- Lockhart et al., "Expression monitoring by hybridization to high-density oligonucleotide arrays," *Nat. Biotech.* 14:1675-1680 (1996).
- Logue et al., "General Approaches to Mask Design for Binary Optics," *SPIE*, 1052:19-24 (1989).
- Loken et al., "three-color Immunofluorescence Analysis of Leu Antigens on Human Peripheral Blood Using Two Lasers on a Fluorescence-Activated Cell Sorter," *Cytoetry*, 5:151-158 (1984).
- Love et al., "Screening of λ Library for Differentially Expressed Genes Using in Vitro Transcripts," *Anal. Biochem.*, 150:429-441 (1985).
- Lowe, C.R., "Biosensors," *Trends in Biotech.*, 2:59-65 (1984).
- Lowe, C.R., "An Introduction to the Concepts and Technology of Biosensors," *Biosensors*, 1:3-16 (1985).
- Lowe, C. R., *Biotechnology and Crop Improvement and Protection*, BCPC Publications, pp. 131-138 (1986).
- Lowe et al., "Solid-Phase Optoelectronic Biosensors," *Methods in Enzymology*, 137:338-347 (1988).
- Lowe, C.R., "Biosensors," *Phil. Tran. R. Soc. Lond.*, 324:487-496 (1989).
- Lu et al., "Differential screening of murine ascites cDNA libraries by means of in vitro transcripts of cell-cycle-phase-specific cDNA and digital image processing," *Gene*, 86:185-192 (1990).
- Luo, J. et al., "Improving the fidelity of *Thermus thermophilus* DNA ligase," *NucAcids Res.*, 24(14):3071-3078 (1996).
- Lysov et al., "A new method for determining the DNA nucleotide sequence by hybridization with oligonucleotides," *Doklady Biochem.*, 303(1-6):436-438 (1989).
- Lysov et al., "DNA Sequencing by Oligonucleotide Hybridization," First International Conference on Electrophoresis, Supercomputing and the Human Genome, 4/10-13/90 p. 157.
- MacDonald et al., "A Rapid ELISA for Measuring Insulin in a Large Number of Research Samples," *Metabolism*, 38(5):450-452 (1989).
- Mairanovsky, V.G., "Electro-Deprotection-Electrochemical Removal of Protecting Groups**," *Angew. Chem. Int. Ed. Engl.*, 15(5):281-292 (1976).
- Manz et al., "Miniaturized Total Chemical Analysis Systems: a Novel Concept for Chemical Sensing," *Sensors and Actuators*, B1:244-248 (1990).
- Manz et al., "Micromachining of monocrystalline silicon and glass for chemical analysis systems, A look into next century's technology or just a fashionable craze?," *Trends in Analytical Chem.*, 10(5):144-149 (1991).
- Manz et al., "Planar chips technology for miniaturization and integration of separation techniques into monitoring systems, Capillary electrophoresis on a chip," *J. Chromatography*, 593:253-258 (1992).
- Manz et al., "Planar Chips Technology for Miniaturization of Separation Systems: A Developing Perspective in Chemical Monitoring," chapter 1, 1-64 (1993).
- Manz et al., "Electroosmotic pumping and electrophoretic separations for miniaturized chemical analysis systems," *J. Micromech. Microeng.*, 4:257-265 (1994).
- Masiakowski et al., "Cloning of cDNA sequences of hormone-regulated genes from the MCF-7 human breast cancer cell line," *Nuc. Acids Res.*, 10(24):7895-7903 (1982).
- Matsumoto et al., "Preliminary Investigation of Micropumping Based on Electrical Control of Interfacial Tension," *IEEE*, pp. 105-110 (1990).
- Matsuzawa et al., "Containment and growth of neuroblastoma cells on chemically patterned substrates," *J. Neurosci. Meth.*, 50:253-260 (1993).
- Matthes et al., "Simultaneous rapid chemical synthesis of over one hundred oligonucleotides on a microscale," *EMBO J.*, 3(4):801-805 (1984).
- McCray et al., "Properties and Uses of Photoreactive Caged Compounds," *Ann. Rev. Biophys. Biophys. Chem.*, 18:239-270 (1989).
- McGall et al., "The Efficiency of Light-Directed Synthesis of DNA Arrays on Glass Substrates," *J. American Chem. Soc.*, 119(22):5081-5090 (1997).
- McGillis, VLSI Technology, Sze, eds., Chapter 7, "Lithography," pp. 267-301 (1983).
- McMurray, J.S., "Solid Phase Synthesis of a Cyclic Peptide Using Fmoc Chemistry," *Tetrahedron Letters*, 32(52):7679-7682 (1991).
- Meinkoth et al., "Review: Hybridization of Nucleic Acids Immobilized on solid Supports," *Analytical Biochem.*, 138:267-284 (1984).
- Melcher et al., "Traveling-Wave Bulk Electroconvection Induced across a Temperature Gradient," *Physics of Fluids*, 10(6):1178-1185 (1967).
- Merrifield, R.B., "Solid Phase peptide Synthesis. I. The Synthesis of a Tetrapeptide," *J. Am. Chem. Soc.*, 85:2149-2154 (1963).
- Michiels et al., "Molecular approaches to genome analysis: a strategy for the construction of ordered overlapping clone libraries," *CABIOS*, 3(3):203-10 (1987).
- Mirzabekov, A.D., "DNA sequencing by hybridization—a megasequencing method and a diagnostic tool?," *TIBTECH*, 12:27-32 (1994).
- Miyada et al., "Oligonucleotide Hybridization Techniques," *Meth. Enzymology*, 154:94-107 (1987).
- Monaco et al., "Human Genome Linking with Cosmids and Yeast Artificial Chromosomes," abstract from CSHS, p. 50, (1989).
- Morita et al., "Direct pattern fabrication on silicone resin by vapor phase electron beam polymerization," *J. Vac. Sci. Technol.*, B1(4):1171-1173 (1983).
- Morrison et al., "Solution-Phase Detection of Polynucleotides Using Interacting Fluorescent Labels and Competitive Hybridization," *Anal. Biochem.*, 183:231-244 (1989).
- Munegumi et al., "thermal Synthesis of Polypeptides from N-Boc-Amino Acid (Aspartic Acid, β -Aminoglutaric Acid) Anhydrides," *Chem. Letters*, pp. 1643-1646 (1988).
- Mutter et al., "Impact of Conformation on the Synthetic Strategies for Peptide Sequences," pp. 217-228 from Chemistry of Peptides and Proteins, vol. 1, Proceedings of the Third USSR-FRG Symp., in USSR (1982).
- Nakamori et al., "A Simple and Useful Method for Simultaneous Screening of Elevated Levels of Expression of a Variety of Oncogenes in Malignant Cells," *Jpn. J. Cancer Res.*, 79:1311-1317 (1988).

IAFP00000662

- Nederlof et al., "Multiple Fluorescence In Situ Hybridization," *Cytometry*, 11:126-131 (1990).
- Nederlof et al., "Three-Color Fluorescence In Situ Hybridization for the Simultaneous Detection of Multiple Nucleic Acids Sequences," *Cytometry*, 10:20-27 (1989).
- Nizetic et al., "An improved bacterial colony lysis procedure enables direct DNA hybridisation using short (10, 11 bases) oligonucleotides to cosmids," *Nuc. Acids Res.*, 19(1):182 (1990).
- Nizetic et al., "Construction, arraying, and high-density screening of large insert libraries of human chromosomes X and 21: their potential use as reference libraries," *PNAS*, 88:3233-3237 (1991).
- Nyborg, W., "Acoustic Streaming," chapter 11 pp. 265-329 from *Physical Acoustics, Principles and Methods*, Mason, eds., vol. II, part B, Academic Press, New York and London (1965).
- Ocvirk et al., "High Performance Liquid Chromatography Partially Integrated onto a Silicon Chip," *Analyt. Meth. Instrumentation*, 2(2):74-82 (1995).
- Ohtsuka et al., "Studies on transfer ribonucleic acids and related compounds. IX Ribonucleic oligonucleotide synthesis using a photosensitive 0-nitrobenzyl protection at the 2'-hydroxyl group," *NucAcidsRes.*, 1(10):1351-1357 (1974).
- Olefirowicz et al., "Capillary Electrophoresis for Sampling Single Nerve Cells," *Chimia*, 45(4):106-108 (1991).
- Olson et al., "Random-clone strategy for genomic restriction mapping in yeast," *PNAS*, 83:7826-7830 (1986).
- Patchornik et al., "Photosensitive Protecting Groups," *J. Am. Chem. Soc.*, 92(21):6333-6335 (1970).
- Patent Abstracts of Japan from EPO, Abst. 13:557, JP 1-233 447 (1989).
- Pease et al., "Light-generated oligonucleotide arrays for rapid DNA sequence analysis," *PNAS*, 91:5022-26 (1994).
- Pevzner, P.A., "DNA Physical Mapping and Alternating Eulerian Cycles in Colored Graphs," *Algorithmica*, 13(1-2):77-105 (1995).
- Pevzner et al., "Multiple Filtration and Approximate Pattern Matching," *Algorithmica*, 13(1-2):135-154 (1995).
- Pevzner et al., "Generalized Sequence Alignment and Duality," *Adv. Applied Math.*, 14:139-171 (1993).
- Pevzner, P.A., "1-Tuple DNA Sequencing: Computer Analysis," *J. Biomol. Struct. Dynam.*, 7(1):63-69 (1989).
- Pfahler et al., "Liquid Transport in Micron and Submicron Channels," *Sensors and Actuators*, A21-A23:431-4 (90).
- Pfeifer et al., "Genomic Sequencing and Methylation Analysis by Ligation Mediated PCR," *Science*, 246:810-813 (1989).
- Pidgeon et al., "Immobilized Artificial Membrane Chromatography: Supports Composed of Membrane Lipids," *Anal. Biochem.*, 176:36-47 (89).
- Pillai, V.N., "Photoremovable Protecting Groups in Organic Synthesis," *Synthesis*, pp. 1-26 (1980).
- Pillai et al., "3-Nitro-4-Aminomethylbenzoyl derivative von Polyethylenglykolen: Eine neue Klasse von Photosensitiven löslichen Polymeren Trägern zur Synthese von C-terminale Peptidamiden," *Tetrah. Lett.*, # 36 p. 3409-3412 (1979).
- Pillai et al., "Synthesis Hydrophilic Polymers, Biomedical and Chemical Applications," *Naturwissenschaften*, 68:558-566 (1981).
- Pirrung et al., "Proofing of Photolithographic DNA Synthesis with 3',5'-Dimethoxybenzoyloxycarbonyl-Protected Deoxynucleoside Phosphoramidites," *J. Org. Chem.*, 63(2):241-246 (1998).
- Pirrung et al., "Comparison of Methods for Photochemical Phosphoramidite-Based DNA Synthesis," *J. Org. Chem.*, 60:6270-6276 (1995).
- Ploax et al., "Cyclization of peptides on a solid support," *Int. J. Peptide Protein Research*, 29:162-169 (1987).
- Polsky-Cynkin et al., "Use of DNA Immobilized on Plastic and Agarose Supports to Detect DNA by Sandwich Hybridization," *Clin. Chem.*, 31(9):1428-1443 (1985).
- Poustka et al., "Molecular Approaches to Mammalian Genetics," Cold Spring Harbor Symposia on Quantitative Biology, 51:131-139 (1986).
- Purushothaman et al., "Synthesis of 4,5-diarylimidazole-2 thiones and their photoconversion to bis(4,5-diarylimidazol-2-yl) sulphides," *Ind. J. Chem.*, 29B:18-21 (1990).
- Quesada et al., "High-Sensitivity DNA Detection with a Laser-Excited Confocal Fluorescence Gel Scanner," *Biotechniques*, 10:616 (1991).
- Reichmanis et al., *J. Polymer Sci. Polymer Chem. Edition*, 23:1-8 (1985).
- Renz et al., "A colorimetric method for DNA hybridization," *Nuc. Acids Res.*, 12(8):3435-3445 (1984).
- Richter et al., "An Electrohydrodynamic Micropump," *IEEE*, pp. 99-104 (1990).
- Richter et al., "Electrohydrodynamic Pumping and Flow Measurement," *IEEE*, pp. 271-276 (1991).
- Richter et al., "A Micromachined electrohydrodynamic (EHD) pump," *Sensors and Actuators*, A29:159-168 (91).
- Robertson et al., "A General and Efficient Route for Chemical Aminoacylation of Transfer RNAs," *J. Am. Chem. Soc.*, 113:2722-2729 (1991).
- Rodda et al., "The Antibody Response to Myoglobin-I. Systematic Synthesis of Myoglobin Peptides Reveals Location and Substructure of Species-Dependent Continuous Antigenic Determinants," *Mol. Immunol.*, 23(6):603-610 (1986).
- Rodgers, R.P., "Data Processing of Immunoassay Results," *Manual of Clin. Lab. Immunol.*, 3rd ed., ch. 15, pp. 82-87 (1986).
- Rose, D.J., "Free-solution reactor for post-column fluorescence detection in capillary zone electrophoresis," *J. Chromatography*, 540:343-353 (1991).
- Rovero et al., "Synthesis of Cyclic Peptides on solid Support," *Tetrahed. Letters*, 32(23):2639-2642 (1991).
- Sambrook, *Molecular Cloning—A Laboratory Manual*, publ. in 1989 (not included).
- Saiki et al., "Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes," *PNAS*, 86:6230-6234 (1989).
- Saiki et al., "Analysis of enzymatically amplified β -globin and HLA-DO α DNA with Allele-specific oligonucleotide probes," *Nature*, 324:163-166 (1986).
- Schafer et al., "DNA fingerprinting using non-radioactive oligonucleotide probes specific for simple repeats," *Nuc. Acids Res.*, 16(19):9344 (1988).
- Scharf et al., "HLA class II allelic variation and susceptibility to pemphigus vulgaris," *PNAS*, 85(10):3504-3508 (1988).

US 6,355,432 B1

Page 10

- Schena et al., "Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes," *PNAS*, 93:10614-10619 (1996).
- Schuup et al., "Mechanistic Studies of the Photorearrangement of o-Nitrobenzyl Esters," *J. Photochem.*, 36:85-97 (1987).
- Seed, B., "Diazotizable arylamine cellulose papers for the coupling and hybridization of nucleic acids," *Nuc. Acids Res.*, 10(5):1799-1810 (1982).
- Seiler et al., "Planar Glass Chips for Capillary Electrophoresis: Repetitive Sample Injection, Quantitation, and Separation Efficiency," *Anal. Chem.*, 65:1481-1488 (1993).
- Seller et al., "Electroosmotic Pumping and Valveless Control of Fluid Flow with a Manifold of Capillaries on a Glass Chip," *Anal. Chem.*, 66:3485-3491 (1994).
- Semmelhack et al., "Selective Removal of Protecting Groups Using Controlled Potential Electrolysis," *J. Am. Chem. Society*, 94(14):5139-5140 (1972).
- Sheldon et al., "Matrix DNA Hybridization," *Clinical Chemistry*, 39(4):718-719 (1993).
- Shin et al., "Dehydrooligonopeptides. XI. Facile Synthesis of Various Kinds of Dihydrodi- and tripeptides, and Dehydroenkephalins Containing Tyr Residue by Using N-Carboxydehydrotyrosine Anhydride," *Bull. Chem. Soc. Jpn.*, 62:1127-1135 (1989).
- Sim et al., "Use of a cDNA Library for Studies on Evolution and Developmental Expression of the Chorion Multigene Families," *Cell*, 18:1303-1316 (1979).
- Smith et al., "A Novel Method for Delineating Antigenic Determinants: Peptide Synthesis and Radioimmunoassay Using the Same Solid Support," *Immunochemistry*, 14:565-568 (1977).
- Sofia, M.J., "Carbohydrate-based combinatorial libraries," *Molecular Diversity*, 3:75-94 (1998).
- Southern et al., "Report on the Sequencing by Hybridization Workshop," *Genomics*, 13:1378-1383 (1992).
- Southern et al., "Oligonucleotide hybridisations on glass supports: a novel linker for oligonucleotide synthesis and hybridization properties of oligonucleotides synthesized in situ," *Nuc. Acids Res.*, 20(7):1679-1684 (1992).
- Southern et al., "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Arrays of Oligonucleotides: Evaluation Using Experimental Models," *Genomics*, 13:1008-10017 (1992).
- Southern, E.M., "Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis," *J. Mol. Biol.*, 98:503-517 (1975).
- Stemme et al., "A valveless diffuser/nozzle-based fluid pump," *Sensors and Actuators*, A39:159-167 (1993).
- Stryer, L., "DNA Probes and Genes Can be Synthesized by Automated Solid-Phase Methods," from *Biochemistry*, Third Edition, published by W.H. Freeman & Co., (1988).
- Stuber et al., "Synthesis and photolytic cleavage of bovine insulin B22-30 on a nitrobenzoylglycyl-poly (ethylene glycol) support," *Int. J. Peptide Protein Res.*, 22(3):277-283 (1984).
- Sundberg et al., "Spatially-Addressable Immobilization of Macromolecules on Solid Supports," *J. Am. Chem. Soc.*, 117(49):12050-12057 (1995).
- Swedberg, S.A., "Use of non-ionic and zwitterionic surfactants to enhance selectivity in high-performance capillary electrophoresis. An apparent micellar electrokinetic capillary chromatography mechanism," *J. Chromatography*, 503:449-452 (1990).
- Thomas, P.S., "Hybridization of denatured RNA and small DNA fragments transferred to nitrocellulose," *PNAS*, 77(9):5201-5205 (1980).
- Titus et al., "Texas Red, a Hydrophilic, red-emitting fluorophore for use with fluorescein in dual parameter flow microfluorometric and fluorescence microscopic studies," *J. Immunol. Meth.*, 50:193-204 (1982).
- Tkachuk et al., "Detection of bcr-abl Fusion in chronic Myelogenous Leukemia by in situ Hybridization," *Science*, 250:559-562 (90).
- Trzeciak et al., "Synthesis of 'Head-to-Tail' Cyclized Peptides on Solid Support by Fmoc Chemistry," *Tetrahed. Letters*, 33(32):4557-4560 (1992).
- Tsien et al., "Control of Cytoplasmic Calcium with Photolabile Tetracarboxylate 2-Nitrobenzhydryl Chelators," *Biophys. J.*, 50:843-853 (1986).
- Tsutsumi et al., "Expression of L- and M- Type Pyruvate Kinase in Human Tissues," *Genomics*, 2:86-89 (1988).
- Turchinskii et al., "Multiple Hybridization in Genome Analysis, Reaction of Diamines and Bisulfate with Cytosine for Introduction of Nonradioactive labels Into DNA," *Molecular Biology*, 22:1229-1235 (1988).
- Turner et al., "Photochemical Activation of Acylated α -Thrombin," *J. Am. Chem. Soc.*, 109:1274-1275 (1987).
- Urdea et al., "A novel method for the rapid detection of specific nucleotide sequences in crude biological samples without blotting or radioactivity; application to the analysis of hepatitis B virus in human serum," *Gene*, 61:253-264 (1987).
- Urdea et al., "A comparison of non-radioisotopic hybridization assay methods using fluorescent, chemiluminescent and enzyme labeled synthetic oligodeoxyribonucleotide probes," *Nuc. Acids. Res.*, 16(11):4937-4956 (1988).
- Van der Voort et al., "Design and Use of a Computer Controlled Confocal Microscope for Biological Applications," *Scanning*, 7(2):66-78 (1985).
- Van Hijfte et al., "Intramolecular 1,3-Diyl Trapping Reactions. A Formal Total Synthesis of -Coriolin," *J. Organic Chemistry*, 50:3942-3944 (1985).
- Veldkamp, W.B., "Binary optics: the optics technology of the 1990s," *CLEO 90*, vol. 7, paper # CMG6 (1990).
- Verlaan-de Vries et al., "A dot-blot screening procedure for mutated ras oncogenes using synthetic oligodeoxynucleotides," *Gene*, 50:313-320 (1986).
- Verpoorte et al., "Three-dimensional micro flow manifolds for miniaturized chemical analysis systems," *J. Micromech. Microeng.*, 4:246-256 (1994).
- Volkmut et al., "DNA electrophoresis in microlithographic arrays," *Nature*, 358:600-602 (1992).
- Voss et al., "The immobilization of oligonucleotides and their hybridization properties," *Biochem. Soc. Transact.*, 16:216-217 (1988).
- Wada, A., *International Workshop on Automatic and High Speed DNA Base Sequencing*, Hayashibara Forum 1987 at Hayashibara Biochemical Laboratories, Okayama, Japan, Jul. 7-9, 1987.
- Walker et al., "Photolabile Protecting Groups for an Acetylcholine Receptor Ligand. Synthesis and Photochemistry of a New Class of o-Nitrobenzyl Derivatives and their Effects on Receptor Function," *Biochemistry*, 25:1799-1805 (1986).

IAFP00000664

US 6,355,432 B1

Page 11

- Wallace et al., "The use of synthetic oligonucleotides as hybridization probes. II. Hybridization of oligonucleotides of mixed sequence to rabbit β -globin DNA," *Nuc. Acids Res.*, 9(4):879 (1981).
- Wallace et al., "Hybridization of synthetic oligodeoxynucleotides to $\Phi\chi$ 174 DNA: the effect of single base pair mismatch," *Nuc. Acids Res.*, 11(6):3543-3557 (1979).
- Washizu et al., "Handling Biological Cells Using a Fluid Integrated Circuit," *IEEE Transactions Industry Applications*, 26(2):352-358 (1990).
- Wiedmann, M. et al., "Ligase Chain Reaction (LCR)—Overview and Applications," *PCR Meth. Appl.*, 3(4):S51-S64 (1994).
- Werner et al., "Size-Dependent Separation of Proteins Denatured in SDS by Capillary Electrophoresis Using a Replaceable Sieving Matrix," *Anal. Biochem.*, 212:253-258 (1993).
- White et al., "An Evaluation of Confocal Versus Conventional Imaging of Biological Structures by Fluorescence Light Microscopy," *J. Cell Biol.*, 105(1):41-48 (1987).
- Widacki et al., "Biochemical Differences in Qa-2 Antigens Expressed by Qa-2+, 6+ and Qa-2a+, 6- Strains. Evidence for Differential Expression of the Q7 and Q9 Genes," *Mol. Immunology*, 27(6):559-570 (1990).
- Wilcox et al., "Synthesis of Photolabile 'Precursors' of Amino Acid Neurotransmitters," *J. Org. Chem.*, 55:1585-1589 (1990).
- Wilding et al., "PCR in a Silicon Microstructure," *Clin. Chem.*, 40(9):1815-1818 (1994).
- Wilding et al., "Manipulation and Flow of Biological Fluids in Straight Channels Micromachined in Silicon," *Clin. Chem.*, 40(1):43-47 (1994).
- Wittman-Liebold, eds., *Methods in Protein Sequence Analysis*, from Proceedings of 7th Int'l Conf., Berlin, Germany, 7/3-8/88, table of contents, pp. xi-xx* (1989).
- Wood et al., "Base composition-independent hybridization in tetramethylammonium chloride: A method for oligonucleotide screening of highly complex gene libraries," *PNAS*, 82:1585-1588 (1985).
- Woolley et al., "Ultra-high-speed DNA fragment separations using microfabricated capillary array electrophoresis chips," *PNAS*, 91:11348-11352 (1994).
- Wu et al., "Synthesis and Properties of Adenosine-5'-triphospho- γ -5-(5-sulfonic acid)naphthyl Ethylamide: A Fluorescent Nucleotide Substrate for DNA-Dependent RNA Polymerase from *Escherichia coli*," *Arch. Biochem. Biophys.*, 246(2):564-571 (1986).
- Wu et al., "Laboratory Methods, Direct Analysis of Single Nucleotide Variation in Human DNA and RNA Using In Situ Dot Hybridization," *DNA*, 8(2):135-142 (1989).
- Yamamoto et al., "Features and applications of the laser scanning microscope," *J. Mod. Optics*, 37(11):1691-1701 (1990).
- Yarbrough et al., "Synthesis and Properties of Fluorescent Nucleotide Substrates for DNA-dependent RNA Polymerases," *J. Biol. Chem.*, 254(23):12069-12073 (1979).
- Yosomiya et al., "Performance, Glass fiber Having Isocyanate Group on the Surface. Preparation and Reaction with Amino Acid," *Polymer Bulletin*, 12:41-48 (1984).
- Young, W.S., "Simultaneous Use of Digoxigenin- and Radiolabeled Oligodeoxynucleotide Probes for Hybridization Histochemistry," *Neuropeptides*, 13:271-275 (1989).
- Yue et al., "Miniature Field-Flow Fractionation System for Analysis of Blood Cells," *Clin. Chem.*, 40(9):1810-1814 (1994).
- Zehavi et al., "Light-Sensitive Glycosides. I. 6-Nitroveratryl β -D-Glucopyranoside and 2-Nitrobenzyl β -D-Glucopyranoside," *J. Org. Chem.*, 37(14):2281-2285 (1972).
- Zengerle et al., "Transient measurements on miniaturized diaphragm pumps in microfluid systems," *Sensors and Actuators*, A46-47:557-561 (1995).
- Zischler et al., "Non-radioactive oligonucleotide fingerprinting in the gel," *Nuc. Acids Res.*, 19(11):4411 (1989).
- Zischler et al., "Digoxigenated oligonucleotide probes specific for simple repeats in DNA fingerprinting and hybridization in situ," *Hum. Genet.*, 82:227-233 (1989).
- Hodgson et al., *Nucl. Acids Res.*, 15(15):6295 (1987).
- Khrapko et al., *DNA Seq. Map*, 1:375-388 (1991).
- Lander et al., *Genomics*, 2:231-239 (1988).
- Little, *Nature*, 346:611-612 (1990).
- Lysov et al., *Dokl. Akad. Nauk. SSSR*, 303:1508-1511 (1988).
- Olson et al., *Proc. Natl. Acad. Sci. USA*, 83:7826-7830 (Oct. 1986).
- Pevzner, *Algorithmica*, 13(1-2):77-105 (1995).
- Pevzner et al., *Algorithmica*, 13(1-2):135-154 (1995).
- Pfeifer et al., *Science*, 246:810-813 (Nov. 10, 19889).
- Seed, *Nucl. Acids Res.*, 10(5):1799-1810 (1982).
- Wood et al., *Proc. Natl. Acad. Sci. USA*, 82:1585-1588 (1985).
- Feinberg et al., *Anal. Biochem.*, 137:266-267 (1984).
- Pevzner et al., *Adv. Applied Math.*, 14:139-171 (1993).
- Schena et al., *Proc. Natl. Acad. Sci. USA*, 93:10614-10619 (Oct. 1996).
- Miller et al., "Detection of bacteria by hybridization of rRNA with DNA-latex and immunodetection of hybrids" *J Clin Microbiol* 1988, 26:1271-1276.
- Brenner et al., "In vitro cloning of complex mixtures of DNA on microbeads: Physical separation of differentially expressed cDNAs," *PNAS*, vol. 97, No. 4, Feb. 15, 2000, pp. 1665-1670.
- Brenner et al., "Gene expression analysis by massively parallel signature sequencing (MPSS) on microbead arrays," *Nature Biotechnology*, vol. 18, Jun. 2000, pp. 630-634.
- Tyagi, "Taking a census of mRNA populations with microbeads," *Nature Biotechnology*, vol. 18, Jun. 2000, pp. 597 and 598.

U.S. Patent

Mar. 12, 2002

Sheet 1 of 2

US 6,355,432 B1

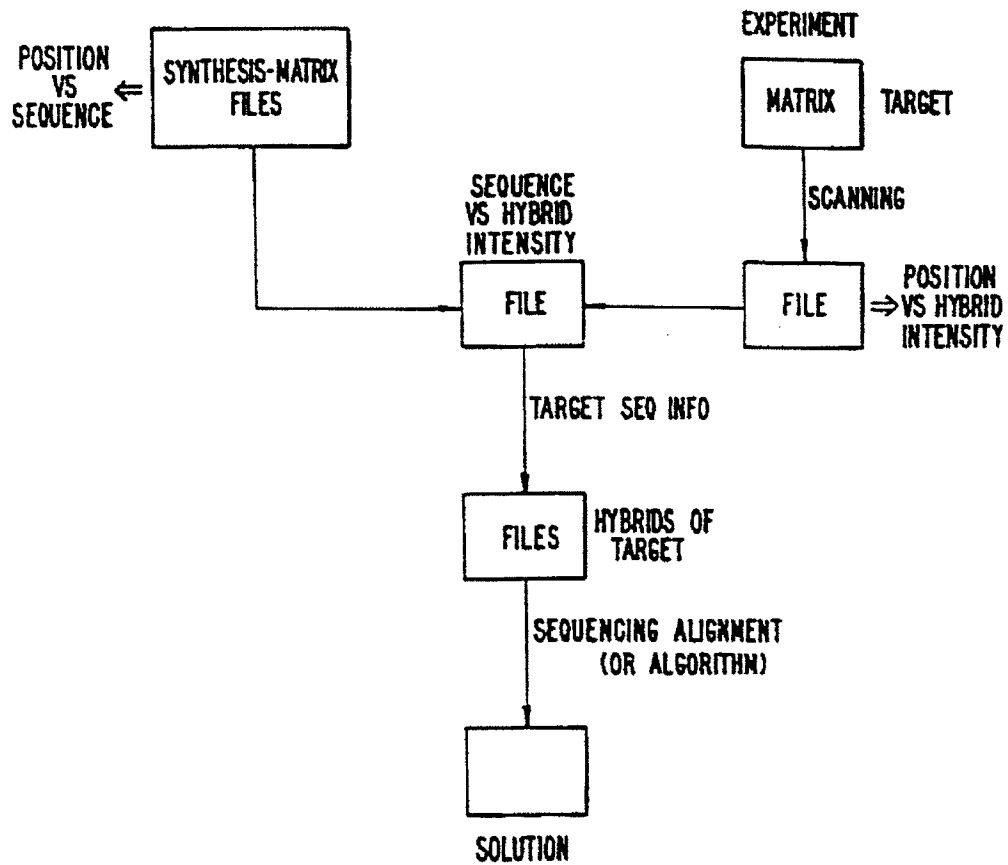


FIG. 1

U.S. Patent

Mar. 12, 2002

Sheet 2 of 2

US 6,355,432 B1

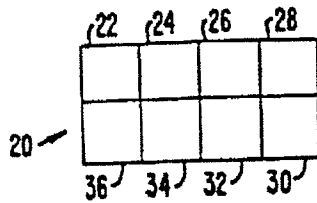


FIG. 2A

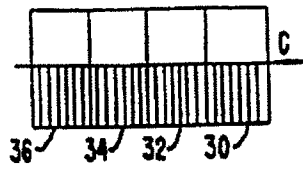


FIG. 2B

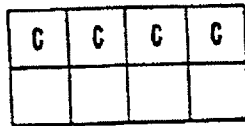


FIG. 2C

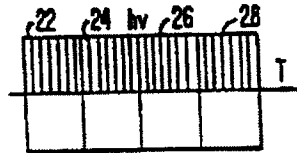


FIG. 2D

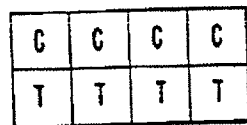


FIG. 2E

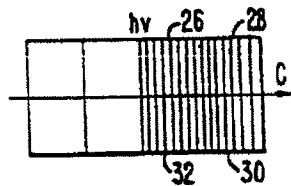


FIG. 2F

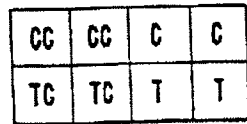


FIG. 2G

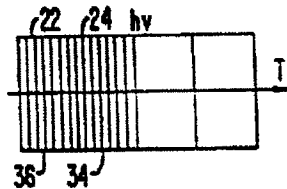


FIG. 2H

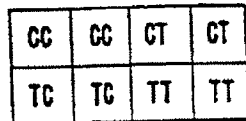


FIG. 2I

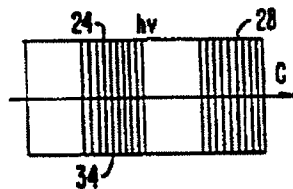


FIG. 2J

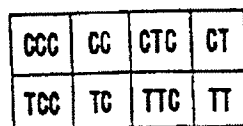


FIG. 2K

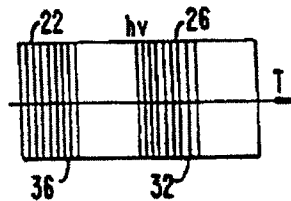


FIG. 2L

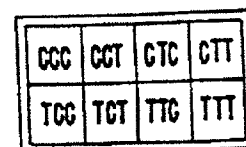


FIG. 2M